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UiO : University of Oslo

Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2021

RIIM

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Pages

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

As for all other parts of society, RIIM has been influenced by the Covid-19 pandemic also during 2021. The pandemic results in new research opportunities, and several groups at RIIM are involved in the important task of collection and analysis of patient materials from patients suffering from Covid-19, and many important publications about Covid-19 have already been published originating from RIIM. The biobank with material from these patients will in the coming years prove to be valuable for further understanding of the pandemic as well as helping us meeting future challenges in a better way. Although much resources and personnel have been allocated to Covid-19 research, the institute have still been able to regain momentum in our "normal" research an publish high quality research.

In Norway, we were so fortunate that we already in early 2021 had access to vaccines against Covid-19. But during the spring 2021, Norway and Denmark stopped the ChAdOx1 nCoV-19 vaccination after several reported cases of vaccine-induced syndrome of severe thrombosis and thrombocytopenia (VITT) with fatal outcome. Through an intensive collaboration with other milieus at the hospital, several researchers from RIIM were heavily involved in this work, linking the severe outcomes to this specific vaccine helping the government decide to halt the use of this vaccine. Further, several groups at RIIM were also involved in a more detailed description of the underlying mechanisms in this VITT suggesting that antibody-mediated thrombus formation in VITT patients is accompanied by a massive innate immune activation with activation of neutrophils, at least partly induced by IC-mediated mechanisms with NET formation as a major pathogenic event. This work is a prime example of translational research, where the proximity and collaboration between clinicians and the basal researchers prove its importance for altering the patient treatment, in this case stopping the use of a specific vaccine.

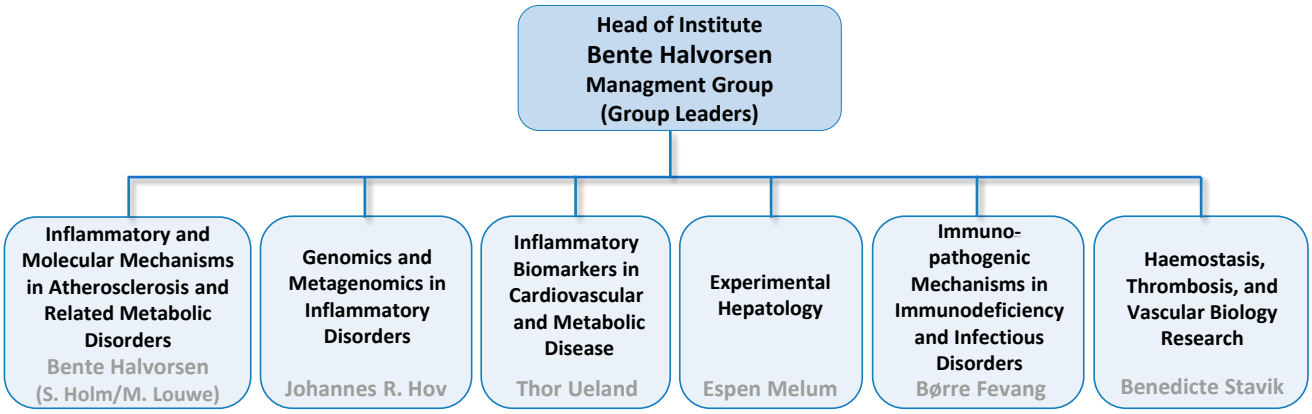
As scientists we have a responsibility towards the society to convey our research. During 2021, researchers from RIIM (Xiang Yi Kong, Ida Gregersen and Maria Belland Olsen), have established the podcast "***Labprat***" where they every week present research from RIIM in a form accessible for all. The podcast is free and available on most platforms and have during the year become among the most popular in the field of medical sciences here in Norway.

OUS is moving forward in planning of the new hospital. This is an important process for the future quality of the health care both in Oslo and Norway. For RIIM, this process is challenging, as it raises uncertainties of our final location and how our work will be possible during the process of building the new hospital. Thus, many of us here at RIIM spend a lot of time planning for the new hospital, ensuring that we also in the future will be properly rigged to do our research. "C1 rokade", the first stage in the OUS 2030, has been planned during 2021 and will affects us the next years to come.

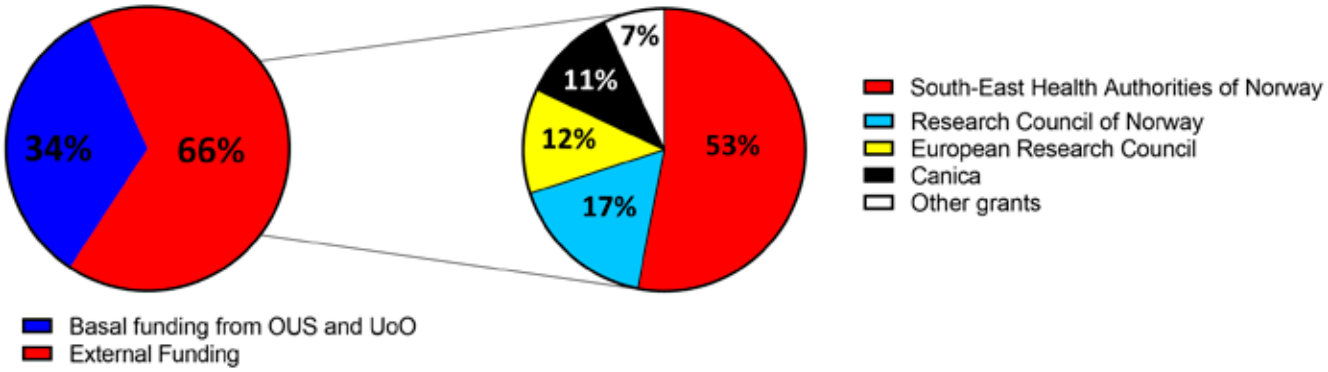
As always, the most challenging situation for RIIM is the economic situation, as we are completely dependent upon external financing. Like previous years, also in 2021 RIIM scientists were granted large research funds, enabling us to do our research and publish high quality papers. During 2021 several groundbreaking papers were published, like Prof. Tom Hemmings Karlsen`s Lancet paper in the end of 2021 and Dr. Holm et al - and Dr. Schultz et al. vaccine papers in prestigious journals. In sum, 2021 RIIM scientist published the highest number of publications ever.

Looking further into 2022 – we know that pandemics is still ongoing - and there is a dark, dark cloud of war above Europe. In spite these challenges, RIIM`s outmost important role is to continue research– and sustain as a robust platform for research and teaching of the next generation scientists. We must keep up the work of financing– and ambition of addition EU fundings. Work for RIIMs lab area in OUS 2030 will be important and challenging and will flavoring the year to come. But most of all, we must still contribute to society and scientific impact of our translational research. Thanks to all RIIM personal – in spite of a pandemic and restrictions, you have all contributed to fantastic scientific 2021.

ORGANIZATION



ECONOMY / FUNDING



The institute's total funding amounted to NOK 63,4 mill in 2020. NOK 36,6 mill (58%) was funds from external sources, while NOK 26,8 mill (42%) was from Oslo University Hospital and University of Oslo. The contributions from external sources are shown in the chart to the right.

FOCUS AREA

Discovery of VITT, a severe side effect of the AstraZeneca COVID-19 vaccine. Truely collaborational, translational, bedside-to-bench research:

By Annika Elisabet Michelsen

From late December 2020, less than a year after the onset of the COVID-19 pandemic, elderly and health care workers were offered vaccination against the SARS-CoV2 virus. The two first registered vaccines was based on mRNA technology in contrast to the third one based on a virus vector technology. The clinical trial testing of the third vaccine, popularly called ChAdOx since it is based on chimpanzee adenovirus and developed in collaboration with University of Oxford, had only been performed in persons aged 18-55 and national health authorities in most countries therefore recommended its use only for persons younger than 65. Practically speaking, this resulted in ChAdOx being used for vaccination of rather young, often female, health care workers from 8th February 2021 in Norway.

11th of March, after more than 130 000 doses being administered, Norwegian Institute of Public Health (NIPH) decided to pause the use of ChAdOx due to reports from Denmark and Austria of possible serious adverse reactions. During the next few days five patients, all vaccinated with ChAdOx the last 10 days, were admitted to Rikshospitalet with serious venous thrombosis at unusual places, low platelet count, and in four of the patients also cerebral bleeding. Clinical staff faced a difficult situation with seriously ill patients without knowing the optimal treatment balancing between thrombosis and bleeding. Hematologists and RIIM scientists Pål André Holme and Nina H Schultz contacted several research groups in Norway for help and collected different types of samples from the patients. The Norwegian National Unit for Platelet Immunology at University Hospital of North Norway in Tromsø found remarkably high levels of antibody against platelet factor 4 (PF4) (1), a phenomenon seen only rarely in patients with heparin-induced thrombocytopenia (HIT). At RIIM other projects were put aside to free up capacity to characterize the samples. After some intensive days of working we could in collaboration with research milieus at OUS, UiO and NIPH, outline some characteristics of vaccine induced thrombocytopenic thrombosis (VITT).

The finding of antibodies against PF4 in VITT was published by Greinacher et al (2) at the same time as us and later confirmed also by Scully et al (3). In HIT, antibodies are raised against PF4 which has been conformationally changed by heparin (a negatively charged molecule) to expose a neoepitope in PF4. The a-PF4 antibodies bind to and activate platelets causing thrombosis and dramatic consumption of platelets. But how can the newly vaccinated previously healthy persons with VITT have such antibodies when they have not been exposed to heparin? We expected PF4 to be complexes to, and transformed by, a polyanion and therefore performed an immunoprecipition and subsequent mass spectrometry to analyze the protein content. In the immunocomplex, PF4 was associated with several proteins potentially regulating both inflammation and coagulation. We found high levels of several soluble immunoreactants in circulation, and a thrombus characterized by more neutrophils than observed in other cerebral venous thrombi (4). Importantly, no proteins or peptides related to the vaccine vector or SARS-CoV2 spike protein was detected, neither in immunocomplex nor in thrombus. Moreover, there were findings of neutrophil extracellular traps (NETs) and cell free DNA both in plasma and in thrombus.

Presumably, the rare VITT syndrome causing platelet activation and thrombus formation is accompanied by a massive innate immune activation with particular activation of neutrophils, at least partly induced by immunocomplex-mediated mechanisms with NET formation as a major pathogenic event.

This work emphasizes the benefit and importance of a close contact between clinical and lab researchers to quickly achieve knowledge that in some cases can guide the treatment of patients and hopefully also can be usefully in the future.

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3. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, Goldblatt D, Kotoucek P, Thomas W, Lester W. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384(23):2202-11.

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"The finding that the AstraZeneca vaccine had to be the cause of the severe thrombocytopenia and thrombotic events in the patients admitted was reported widely in the Norwegian press and internationally."

Using gene editing to cure congenital bleeding disorders

By Maria Eugenia Chollet Dugarte and Benedicte Stavik

In contrast to more common diseases that have a complex pathology, monogenic diseases are caused by a single error in a protein coding gene. The error can be a substitution, deletion, or insertion of a nucleic acid base in DNA, leading to impaired activity of the corresponding protein. Monogenic diseases range from asymptomatic to severe, and although many are subjected to treatment there are no cures for these conditions. Until now. The nature of these diseases makes them ideal candidates for gene therapy and, more recently, gene editing.

Congenital factor (F) VII deficiency is one such example. It is a hereditary bleeding disorder similar to the more known Haemophilia, although it is less frequent. As indicated by the name, the genetic error is located in the ***F7*** gene that encodes the pro-coagulant FVII protein. FVII is an important factor in the blood coagulation cascade and its presence has been thought to be essential for human development and survival.

Heterozygous individuals have about 50 % FVII activity and are asymptomatic, while homozygous patients can have less than 1 % of normal activity. Excessive menstrual bleeding in women and muco-cutaneous bleeding (epistaxis, gums bleeding, easy bruising) are common symptoms, while in severe cases intracranial hemorrhage can occur. Generally, FVII deficiency occurs in 1 in every 500.000 individuals, however, it is almost ten times more common in Norway due to a founder effect. Also, almost all patients in Norway has the same mutation. Thus, it is especially relevant to study this disease in Norway.

In our studies, we use CRISPR-Cas9 technology to edit the error in the ***F7*** gene in order to rescue FVII protein activity. With this technology we can target the single base-pair that is wrong and replace the disease-causing nucleic acid base with the correct one. The most frequent FVII mutation in Norway, denoted c.479A>G (DNA) or p.Q100R (protein), has a single nucleotide error at position 479 in the ***F7*** gene, where an adenosine (A) base is exchanged with a guanine (G) base. This results in a change in the codon from CAG, which codes for the amino acid Glutamine, to CGG, which codes for Arginine, and the protein sequence is changed accordingly (Figure 1).

In vitro studies using recombinant expression of FVII carrying this mutation have shown that the mutated protein is not able to fold into the correct 3-dimentional structure, and hence is retained in the endoplasmic reticulum and not secreted. Using a specifically designed guide RNA, we direct the Cas9 to make a double stranded cut at position 479 in the ***F7*** gene, and with a DNA donor template the wrong base, guanine in this case, is replaced by the correct, adenosine, through homology directed repair

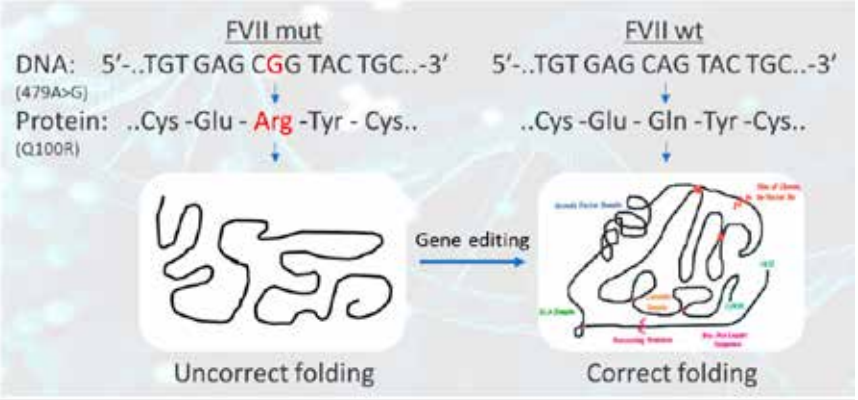

Fig. 1. DNA and protein sequence of FVII with (left) or without (right) the disease-causing mutation.

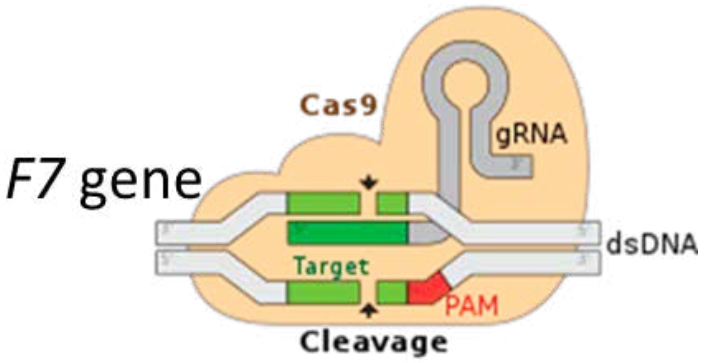

Fig. 2 Illustration of how the Cas9 protein identifies the correct sequence in DNA through base-pairing with the guide RNA.

(Figure 2). This restores the codon sequence, leading to the correct amino acid being inserted and proper folding and secretion of the protein.

Although CRISPR gene editing has been performed directly in a few patients in an ongoing ground-breaking clinical trial to correct blindness, it is still a long way from being used to directly target the patient's liver. Hence, we perform the gene editing in stem cells that we have reprogrammed from blood cells of the patients. Our hospital runs the certified Haemophilia Comprehensive Care Centre for bleeding disorders and all FVII deficient patients are examined and followed up here. This gives us unique access to the whole population of patients in Norway and they are easily recruited by us and our collaborators. Following gene editing, the stem cells are differentiated into liver cells, as this is the site of FVII production in the body, and can be transplanted back to the patient without the risk of rejection. It is essential that only a small increase in protein activity will restore FVII function and ameliorate the bleeding phenotype thus improving the quality of life of these patients. Successful CRISPR-guided base replacement has also been achieved in Espen Melum's group, another team at the RIIM, with promising editing efficacy in both murine embryonic stem cells and human terminally differentiated cells. Thus, the institute now has extensive experience in CRISPR gene editing, applied in different cells, for different diseases.

DISSERTATIONS 2021

Photo: Amalie Huth Hovland, UIO

Hedda Benedicte Hoel

Inflammasome activation, gut microbiota and comorbidities in HIV and COVID-19

3. June 2021

Committee:
1. opponent: Professor Magnus Gisslen, University of Gothenberg, Sahlgrenska Hospital, Sweden
2. opponent: Associate Professor Bjørn Blomberg, University of Bergen, Haukeland University Hospital
3. opponent: Professor Tone Tønjum, University of Oslo

Main supervisor: Associate Professor Marius Trøseid, University of Oslo

Co-supervisor(s): Senior researcher Arne Yndestad; Group leader Børre Fevang

Summary of PhD project:
Despite antiretroviral treatment people with HIV still have a lower life expectancy and increased risk of non-communicable comorbidities such as cardiovascular diseases. Several mechanisms including chronic immune activation, inflammation and traditional risk factors contribute, but exact mechanisms remain elusive. Altered gut microbiota is seen in many diseases including HIV, and lately also COVID-19. Tryptophan metabolism through the kynurenine pathway is of importance in the interplay between microbiota and the immune system. Inflammasome activation is central in the atherogenic pathogenesis, and leads to the release of the proinflammatory cytokines IL-1 and IL-18. These cytokines are tightly regulated, and markers of this activation can be analyzed in plasma.

This thesis aimed to elucidate mechanisms related to microbiota, inflammasome activation and cardiovascular involvement in the RNA viral diseases HIV and Covid-19.

The main findings were that patients that had both HIV and Type 2 diabetes had a reduced gut microbial diversity, higher levels of inflammation and a higher Kynurenine/Tryptophan ratio. Also, tryptophan metabolism was associated with endothelial dysfunction. Furthermore, in a nested case control study, markers of IL-1 activity predicted myocardial infarction in HIV patients up to 10 years before the insult, suggesting the IL-1 system could be an important target for preventive intervention.

In Covid-19 disease respiratory symptoms are most common, but the gut and heart is also affected. In a longitudinal observational study of hospitalized patients with COVID-19, those with cardiac involvement had higher levels of LPS binding Protein and IL-18 suggesting a gut-heart axis in Covid-19, possibly involving inflammasome activation, but further studies are needed.

Photo: Amalie Huth Hovland, UIO

Christiane Mayerhofer, M.D.

Targeting the Gut Microbiota in Heart Failure
November 16, 2021

Committee:
1. opponent: Professor Norbert Frey, Heidelberg University Hospital
2. opponent: Adjunct Professor Ole Fröbert, Örebro University Hospital
3. opponent: Professor Anne Cathrine Staff, University of Oslo

Main supervisor: Associate professor Marius Trøseid, Section of Clinical Immunology and Infectious diseases
Co-supervisor(s): Associate professor Kaspar Broch and Professor Lars Gullestad, Department of Cardiology, and Professor Johannes R. Hov, RIIM

Summary of PhD project:
Although the past decades have seen discoveries that have turned heart failure (HF) into a preventable and partly treatable condition, the syndrome of the failing heart remains incompletely understood. Several components, such as hemodynamic stress, neuroendrocine activation and inflammation, have been implicated

in the progressive deterioration of cardiac function that occurs in HF. Inflammation is of particular interest in this case. Elevated levels of several pro-inflammatory mediators are closely associated with worsening of HF.

Recent research has suggested that the gut microbiota may play a role for the health of the host. The gut microbiota has been linked to various diseases, including HF. In patients with HF, intestinal wall edema due to systemic congestion and reduced intestinal blood flow may increase bacterial translocation into the circulation and induce cytokine production, which is in turn associated with disease progression. In this work, Mayerhofer and colleagues have investigated the gut microbiota in patients with HF and healthy controls through the analysis of fecal and plasma samples. For bacterial analysis, segments of the 16S rRNA marker gene were amplified and submitted to next-generation sequencing. Mayerhofer and colleagues found that the gut microbial profile in patients with chronic heart failure differs from that of healthy controls, and that by-products of microbial metabolism, such as short-chain fatty acids and secondary bile acids, may be relevant for clinical outcomes. They also investigated associations between dietary habits and the gut microbiota, where they found that gut bacterial richness and composition were associated with fiber intake, and that the microbial-dependent metabolite trimethylamine-N-oxide was associated with meat intake. Furthermore, they designed a proof-of-concept trial to target the gut microbiota to improve cardiac function in patients with HF.

Photo: Amalie Huth Hovland, UIO

Cand.med. Natalie Lie Berntsen

The role of natural killer T cells in biliary immunology and disease
June 4, 2021

Committee:
1. opponent: Professor Ye Htun Oo, University of Birmingham, UK
2. opponent: Professor Susanna Cardell, University of Gothenburg, Sweden
3. opponent: Professor Jan Terje Andersen, University of Oslo

Main supervisor: Espen Melum, University of Oslo

Summary of PhD project:
The etiology and pathophysiology of cholangiopathies are mostly unknown and their disease courses are often chronic and progressive due to limited treatment options. The biliary anatomy limits the accessibility to the bile ducts in experimental models and complicates study of biliary immunopathology. The purpose of this thesis was to study the regulatory mechanisms in biliary inflammation, with an emphasis on the role of natural killer T (NKT) cells and the role of lipid antigen presentation in the bile ducts.

We first established a novel bile duct injection model in mice to access the bile ducts for *in vivo* study of biliary immunopathology. This model may be valuable in future studies of normal biliary physiology and different pathophysiological disease mechanisms as it was well tolerated and easily reproducible. NKT cells are activated by lipid antigen presentation by the CD1d-molecule. Cholangiocytes function as antigen presenting cells (APCs) with CD1d-dependent activation of NKT cells *in vitro* and we hypothesized that this immunoregulatory pathway is important in the bile ducts. To explore this, we first demonstrated that intrabiliary injection of the NKT cell-activating agent oxazolone in wild type mice caused an acute cholangitis with activation of NKT cells. *Cd1d*$^{-/-}$ mice that lack NKT cells and wild type mice pretreated with antibody blocking of CD1d were protected from disease. These findings implicate that cells in the bile ducts function as APCs *in vivo* and activate NKT cells in a CD1d-restricted manner.

Finally, we demonstrated the presence of NKT cell-activating antigens in bile from patients with various liver diseases. This may be of importance in biliary immunopathology.

As NKT cells are potent immunomodulators that can act both protective and detrimental in disease, future studies should aim to elucidate this biliary immune pathway as it may expose potentially new therapeutic approaches in cholangiopathies.

Immune regulation in atherosclerosis and other cardio metabolic diseases

Photo: Ine Eriksen, UiO

In front: Turid M Pedersen, Ellen Lund Sagen, Bente Halvorsen, Ana Quiles Jimenez
2nd row: Håvard Foyn, Camilla Huuse, Kari Otterdal, Helene Grannes
3rd row:. Knut Husø Lauritzen, Tuva Børresdatter Dahl, Mieke Louwe, Sarah Murphy, Azita Rashidi
Back: Vigdis Bjerkeli, Sverre Holm, Kuan Yang

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About the group

The overall research focus of our group is on cardiovascular disease and related metabolic diseases such as diabetes, obesity and fatty liver which are major causes of morbidity and mortality worldwide. More specifically, atherosclerosis is a condition characterized by a chronic inflammatory phenotype, while myocardial infarction and stroke, the direct consequences of atherosclerosis, are acute inflammatory conditions. These disorders have many common features, such as dyslipidemia and inflammation. By studying these processes using a translational approach, where we connect basic research and clinic, we want to build a foundation for the development of new diagnostics and treatment for these diseases. Our research group works at the intersection between molecular biology and biochemistry, and cardiovascular, cerebrovascular and endocrine medicine. Our overall goal is to uncover new therapeutic goals and biomarkers. The group uses a wide range of methods, ranging from analysis of patients blood and tissue samples , to studies in genetically modified mice using advanced cell and molecular biology. The group consists of persons with different backgrounds and includes doctors, nutritionists, biochemists, molecular biologists and engineers. This interdisciplinary competence is a great strength of our research group.

Activity in 2021

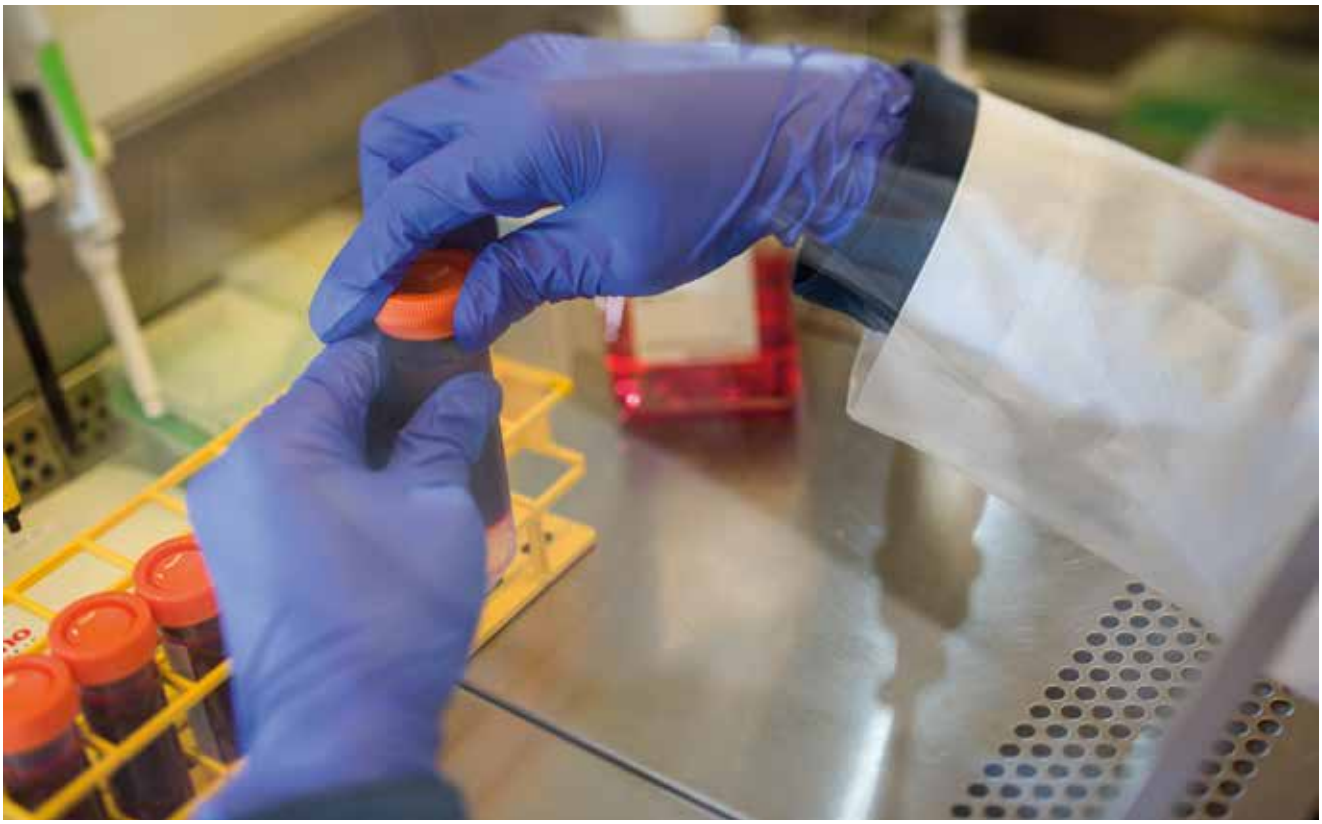
As for all other parts of society, also our research has also this year been influenced by the Covid-19 pandemic. The pandemic results in new research opportunities, as we are involved in the analysis of NorSolidarity, the Norwegian part of the WHO-initiated treatment study of Covid-19 patients. Sequencing and metabolic mapping of the patients are key tasks for personnel in our group and some of the first results indicate that critical Covid-19 is associated with distinct leukocyte phenotypes and transcriptome patterns. The biobank with material from Covid-19 patients will in the coming years prove to be valuable for further understanding of the pandemic.
Despite much focus and effort has been dedicated to these tasks, we have also been able to pursue our regular research ranging from work on human mutations in the Sigirr genes, the role of complement in atherosclerosis, and deciphering the role of ENDOV. Below are some selected examples from advances in some of our projects during 2021:
T cells in obesity We investigate T cell function in metabolic regulation during obesity development to seek new treatment options. T cells can modulate macrophage function and adipocyte differentiation, which affects energy storage and utilization, leading to healthy or dysregulated metabolism. In 2021 we have performed several advanced animal studies leading us closer to pinpoint important mechanisms of how T cells affect whole body metabolism.
EU- projects We are actively participating in two EU projects. During 2021, *AtheroMacHete*, a long lasting project aiming to decipher the heterogeneity of macrophages in atherosclerotic plaques and to determine different functions of the cell types their contribution to disease development came to an end. Another project, *PainFact*, has the objective to investigate the connection of chronic pain, pain sensitivity and development of cardiovascular disease. In 2021 we conducted a large scale animal study to provide data and further material for the whole consortium.

Complications of the Covid vaccines. During spring 2021, Norway and Denmark stopped the ChAdOx1 nCoV-19 vaccination after several reported cases of vaccine-induced syndrome of severe thrombosis and thrombocytopenia with fatal outcome. Through an intensive collaboration with other groups at the hospital, we were heavily involved in this work, which resulted

in a high impact paper that was well received in the scientific community.

Samples from vaccine-induced immune thrombotic thrombocytopenia (VITT) patients allowed us to investigate mechanisms in this severe syndrome and we report immune complexes (ICs) with multi-pathway triggers, innate immune response cytokines, activation of neutrophils in the blood, and extensive formation of neutrophil extracellular traps (NETs) surrounded by IgG in a thrombus ectomized from the sagittal sinus vein. Our results shed light on the underlying mechanisms in this rare adenoviral vector vaccine-induced syndrome of severe thrombosis and thrombocytopenia and suggest that antibody-mediated thrombus formation in VITT patients is accompanied by a massive innate immune activation with particular activation of neutrophils, at least partly induced by IC-mediated mechanisms with NET formation as a major pathogenic event.
Complement activation in cardiovascular disease. Since a couple of years, we are interested in the role the complement pathway plays in cardiovascular disease. By using the biobank of our consultant Mona Skjelland we were able to measure that the complement system is activated in patients with carotid atherosclerosis. Furthermore, we published a paper on a partial activation of this system in heart failure patients.
The role of DNA repair enzymes in cardiovascular disease. For many years we have been studying the DNA Glycosylase, Neil3 and its relation to development of atherosclerosis. During 2021 we have extended our findings in this field by demonstrating that mice deficient in Neil3 have increased gut permeability, which contributes to a pro-atherogenic metabolic phenotype. These findings further demonstrate that Neil3 have functions beyond the traditional role in DNA damage repair.

In another project focusing on DNA damage and cardiovascular disease, we published evidence of a pathophysiological mechanism that connects mitochondrial DNA damage to cardiac dysfunction via reduced NAD+ levels and loss of mitochondrial function and communication. Using a transgenic model, we demonstrate that high levels of cardiomyocyte mtDNA damage cause a reduction in NAD+ levels due to extreme DNA repair activity, causing impaired activation of NAD+-dependent SIRT3, and ultimately mitochondrial dysfunction.



Clinical immunology and infectious diseases

From left: Ingvild Nordøy, Børre Fevang, Magnhild Eide Macpherson, Kari Otterdal and Silje Jørgensen.

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RESEARCH PROFILE

The research group focus on immunopathogenesis in primary and secondary immunodeficiency such as Common variable immunodeficiency (CVID) and HIV and selected infectious diseases, in particular the study of chronic inflammation characterizing these disorders. The aim is to improve the understanding of disease mechanisms and to discover new

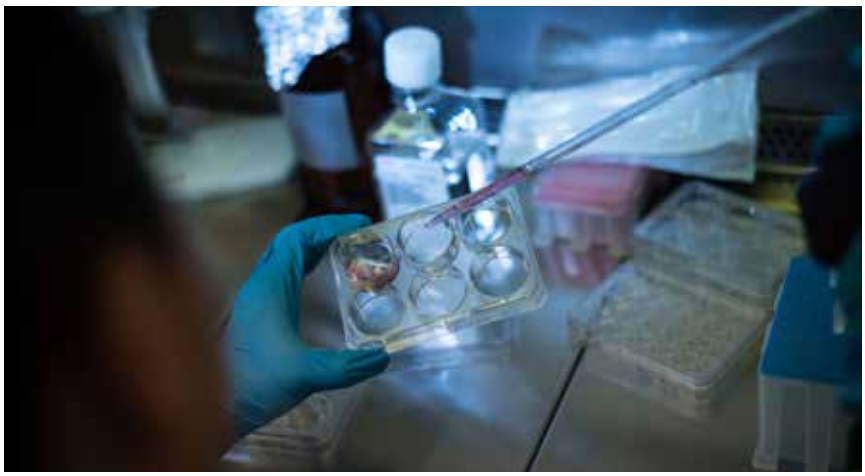
targets for therapeutic intervention. The group works in a translational setting combining close contact to the clinic, in particular Section of Clinical Immunology and Infectious Diseases at OUH, with access to a wide range of immunological methods through extensive collaboration with other groups. Chronic inflammation is a common feature of both immunodeficiencies and many infectious disorders. While inflammation is vital to the clearance of both invading microbes and potentially malignant cells a continued or exaggerated response will further compromise the patient's health. Identifying the factors leading to such an exaggerated response will potentially enable clinicians to modify the inflammatory response of the single patient with agents targeting anything from intracellular signaling pathways to intercellular cytokine networks and microbiota. The group is currently working with several projects, including:

- Immunopathogenic mechanisms in CVID – a disease model for autoimmunity and persistent inflammation. Our group has for a long time used primary immunodeficiency in the form of CVID as a model for studying the immune system. In recent years we have been focusing on the interaction between gut microbiota, gut mucosa and local (intestinal) and systemic inflammation. Magnhild Eide Macpherson has defended her PhD thesis that includes both the modulation of gut microbiota with rifaximin in CVID-patients and an exciting investigation into the anti-inflammatory effect of HDL in the same patients. This latter work is extended into a Post doc project for Silje Fjellgård Jørgensen that started up in 2019 and will include in-depth studies of epigenetic changes in gut mucosa from CVID-patients. We have started a new project focusing on granulomatous-lymphocytic interstitial lung disease (GLILD) in CVID where Mai Sasaki Aanensen Fraz has looked into differences between patients with stable and progressive disease. This project will include collaboration with several Nordic centers with our research group leading the network.

- Targeting the NLRP3 inflammasome in HIV infection. The research institute has a strong track record on HIV-research and this has been continued with Hedda Hoel's PhD project that have looked at the NLRP3 inflammasome as a driving force of the systemic inflammation seen in HIV-infected patients. Hoel successfully defended her PhD in June, with a thesis that also included work on Covid-19. The NLRP3 inflammasome has been studied in cardiovascular disease by other groups at our institute, and the current project is an excellent example of how immunological insight gained from the study of one disease can be applied to new diagnoses. The project is led by Marius Trøseid who is also the main supervisor.

- Functional consequences of novel genetic variations in primary immunodeficencies and immune dysregulation (FUNPID). High-throughput sequencing has revolutionized the diagnostics of primary immunodeficiencies, giving a definite genetic diagnosis in complicated clinical cases. However, novel genetic v ariations of uncertain significance tend to show up and in close collaboration with established partners at Oslo University Hospital and the University of Oslo we have established a research-based diagnostic pipeline for these patients. These findings give us an extraordinary opportunity to characterize both new disease entities and new immunologic mediators. We are currently looking into a family with a possible gain-of-function mutation in IL-1R8.

FUNDING
The group is currently mainly funded through grants from the South-Eastern Norway Regional Health Authority but has also funding from the Anders Jahre foundation, Unifor and the Odd Fellow foundation.



Inflammatory biomarkers in cardiovascular and metabolic disease

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RESEARCH PROFILE

Many disease states are associated with low-grade chronic inflammation that may result in changes in inflammatory proteins in biological fluid such as serum and plasma. Measurement of these biomarkers may therefore be useful for detecting diseases before they present and/or offer information on the mechanisms of disease and treatment targets, or be helpful in evaluating treatment responses and predicting outcomes.

A corner stone in our research is the close collaboration with the Department of Cardiology, and evaluation of biomarkers in heart failure, acute coronary syndromes and aortic stenosis. Biomarkers reflect a wide range of inflammatory processes in the patients and can further predict adverse outcome and treatment responses.

We are evaluating the impact of systemic inflammation in pregnancy on future cardiovascular and metabolic risk together with the Department of Obstetrics. The project "Regulation of non-coding RNAs in preeclampsia (PE) and impact on future cardiovascular risk" was started in 2020 by Tove Lekva with grants from the Norwegian Health Association in collaboration with the Department of Obstetrics, Norwegian Institute of Public Health and the Department of Cardiology. Our hypothesis is that non-coding RNA is crucial for both development of PE and later development of cardiovascular disease. Hopefully our research will lead to an early prediction and better monitoring of this condition, in addition to possible new treatment opportunities, and more understanding of the mechanisms of non-coding RNA in the development of preeclampsia and cardiovascular disease.

The endocrine unit is a part of the research group. The main research focuses on the molecular characterization of the pituitary adenomas and finding novel biomarkers to predict the aggressiveness and recurrence, or the response to medical treatment. In addition, we carry several projects on the role of the adipose tissue and bone on the glucose metabolism and cardiovascular risk in different endocrine diseases.

Severe mental disorders like schizophrenia and bipolar disorders are major contributors of morbidity globally and is associated with both cardiovascular and cancer disease. Together with the Norwegian Centre for Mental Disorders Research (NORMENT) we have for more than 10 years analyzed levels of inflammatory molecules in circulation and demonstrated dysregulation of immune cells and endothelial cells. More recently the use of induced pluripotent stem cell (iPSC) models have enabled more mechanistic studies of how brain cells function in mental disorders.

The newly initiated ALPHA2PREVENT will study if delirium can be prevented in patients undergoing open heart surgery. All five Norwegian heart surgery centers participate and patients will be randomized to receive a_2-adrenergic agonists or placebo. Biomarkers in plasma reflecting neuronal damage will be measured and related to possible development of delirium during the first week post-operatively, but also to declining cognitive and motoric function, and mortality during the next six months.

We have an ongoing strong collaboration with TREC, a translational research center at the University of Tromsø, focusing on patient-oriented and population-based research to reveal new risk factors and mechanisms for the formation of venous thrombosis.

In addition, we have strong collaborations with other clinical research, national and international projects.

EXAMPLES OF ACTIVITY IN 2021

Also in 2021 our attention has been drawn to the COVID-19 pandemic, resulting in several published papers focusing on biomarkers associated with poor prognosis in hospitalized patients. This work is in collaboration with other research groups at RIIM as well as national and international collaborating hospitals and research units

We have continued our effort to identify biomarkers that give useful clinical information on prognosis in patients with cardiovascular disease, but also exciting data in pathophysiological context. In patients with precapillary pulmonary hypertension, a progressive pulmonary vascular disease that can lead to right ventricular failure and subsequent death, we found marked upregulation in circulating levels of several Wnt proteins, and strong associations with long-term poor prognosis. In particular, dysregulation of the Wnt ligand Wnt5a and the secreted endogenous antagonist DKK3 could be implicated in the pathogenesis of precapillary PH.

When investigating PE patient materials we found signs of

dysfunctional telomerase complex and low levels of the long non-coding RNA "TERC" in leukocytes, in addition to elevated telomere associated senescence markers in plasma. The work is progressing with other interesting non-coding RNAs being investigated in leucocytes as well as in plasma extracellular vesicles from these patients.

We have recently described TGF-BR3L - an uncharacterised pituitary specific membrane protein detected in the gonadotroph cells in non-neoplastic and tumour tissue. During the last year, in addition to performing a RNA seq study in tumour samples from patients, we have carried out in vitro studies in mouse gonadotroph cells to further search for the role of TGFBR3L.

In the metabolic research project we have measured circulating adipo- and cytokines in patients with acromegaly and identified novel biomarkers of diseases activity.

Neuron specific enolase (NSE) is an enzyme participating in the glucose metabolism of the brain. Increased levels in plasma is considered a marker of brain injury or degenerative disorders, but on the contrary decreased levels might reflect immature neuronal development. Our study provides further support of a neurodevelopmental rather than a neurodegenerative mechanism in severe mental illness

Genomics and metagenomics in inflammatory diseases

From left: Mikal J Hole, Sajan Raju, Liv Wenche Thorbjørnsen, Johannes R Hov, Kristian Holm, Peder Braadland, Petra Hradicka (back), Hanne Guldsten (front), Marian Maseng, Beate Vestad, Simen H Hansen, Katrine Engesæter, Brian Chung. Photo: private

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how the human genome and the gut microbiome influence inflammatory disease. We do this by applying modern genotyping and sequencing technologies, as well as metabolomics. Increasingly, experimental approaches in vitro and in vivo (mouse models) are also relevant.

Our main interest is primary sclerosing cholangitis, a disease of the bile ducts of the liver, but we are also involved in research in multiple other conditions relevant for the institute, including heart failure and immunodeficiencies. Our main human materials are blood and fecal samples, which we use for genetic (microbiome) and/or metabolomic analyses, but we are also establishing animal models of bile duct disease in the germ-free unit, in collaboration with Melum group.
In 2021, the final version of our first study of full metagenome sequencing (i.e. the study of all microbial genes) was published in Gastroenterology. We found evidence that microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 potentially of microbial origin as a particularly interesting topic. We follow up on these to establish the clinical impact of vitamin B6 in PSC and we have now received a grant to set up a clinical trial focusing on translational aspects of vitamin B6 supplementation. This represents an example on how we work to identify and potential treat altered microbial functions, defining their clinical impact as biomarkers or in therapy. We are applying this methodology also on recurrence of PSC after liver transplantation, which is a significant clinical problem. This is the underlying idea of the ERC Starting Grant project *StopAutoimmunity*, which directs many of the priorities in the group. With increasing data size and complexity, we increasingly depend on bioinformatics and statistics. In our IBD focused projects, where we have used 2021 to perform microbiota profiling of >1000 samples in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we can now apply more advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The groups also work more disease independent with *Clinical microbiota medicine*, as part of a Strategic research area at Oslo University Hospital awarded to the group in 2019. Interventions targeting the gut microbiome to treat disease may provide evidence of causal relationships between the gut microbiome and disease. In 2021, MD Cristiane Mayerhofer (co-supervised by group leader Hov) defended her thesis "Targeting the Gut Microbiota to Treat Heart Failure" on this topic. Also in 2021, a unit and donor bank for fecal microbiota transplants was formally established at Department of Transplantation. Finally, the annual National Microbiota conference was a success, this time in a hybrid format.

FUNDING

The people in the group were in 2021 funded by one ERC Starting Grant, five PhD or postdoc grants and one network grant from Regional Health Authorities of South Eastern Norway, one PhD student following an industrial PhD scheme (funded by Research Council of Norway), one Strategic research area grant in Oslo University Hospital, in addition to Canica, funding one bioinformatician, and Nordforsk. In a collaboration with the Experimental group and partners from the Baltic area (driven from Lithuania) we also received from 2021 funding from the EEA Baltic research funds, which will fund one post doc starting early 2022.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group has extensive collaborations ongoing within NoPSC and the Research Institute of Internal Medicine, multiple clinical research groups (including in particular the IBD group at the Ullevål campus) as well as pathology and radiology. Regionally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator. After a digital only conference in 2020, we successfully hosted the eight national conference on gut microbiota as a hybrid event in November 2021.
Internationally, we continue strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish and German groups.

The Experimental liver research group

From left: Markus Jördens, Espen Melum, Anna Frank, Enya Amundsen-Isaksen, Kari Otterdal, Kathrine Sivertsen Nordhus, Tine Simensen Oldereid, Xiaojun Jiang.

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The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2021 the group consisted of the group leader, three senior researchers, three postdocs, five PhD students, the lab manager, one full-time technician and one part-time technician. Following Anne Pharo's retirement, Oda Helgesen Ramberg took over the lab-manager responsibility. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome. In 2021 our use of techniques from regenerative medicine further increased and we also started using sequencing-based methodologies. Together with patient material, animal models and in vitro assays these additional techniques give us a comprehensive and complete scientific toolbox for achieving our aims.

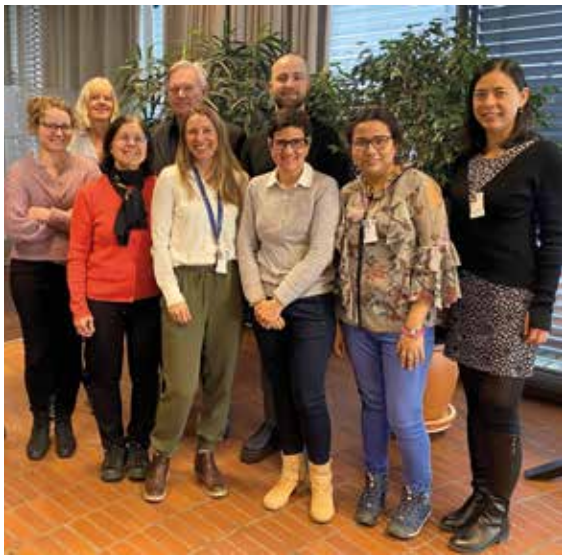
During the last years one of our major lines of research has been to clarify the regulatory role of unconventional T-cells in bile duct inflammation and in 2021 we published a report demonstrating the presence of antigens activating natural killer T (NKT)-cells in bile. Similarly, we also demonstrated in another project that antigens for mucosal associated invariant T (MAIT)-cells are also present in bile and are defined by the microbiome. The role of the immune system during cholestasis has been a key interest in the team focusing on NKT-cells and in 2021 we expanded these projects by investigating the temporal and spatial development and specifically the contribution of the immune system using tissue transcriptomics. Another major topic of our immunology studies has been the role of CD100, which we have found to regulate cholangitis in a familiar form of PSC, and in 2021 a large collaborative paper reporting on a novel mutation in CD100 causing disease in mice and humans were published in Science Translational Medicine. In our studies using germ-free animals we have performed a range of large animal experiments to evaluate the effect on bacterial metabolites on immune system development. To aid the characterization of immune cells from these mice we have started using high-dimensional flowcytometry with 25-colors using the BD Symphony located at the flow-cytometry core facility. The organoid and bile-duct-on-a-chip projects were further strengthened last year by the recruitment of Enya Amundsen-Isaksen as an engineer and the recruitment for the first postdoc in the Research Council of Norway funded project DUCTchip was initiated at the end of the year.

A major event for the group was the excellent defense and celebration of Natalie Lie Berntsen's thesis on June 4th with the title "*The role of natural killer T cells in biliary immunology and disease".* Professor Ye Oo from the University of Birmingham acted as the first opponent and Professor Susanna Cardell for the University of Gothenburg as the second opponent, and their complementary background in NKT-cells, immunology in general and hepatology led to a very interesting discussion. After being awarded a combined position with research and clinical work from her department, previous PhD student Elisabeth Schrumpf rejoined the group to work on unconventional T-cells in our ongoing projects, while at the same time developing her own research agenda related to unconventional T-cells and skin inflammation. 2021 also marked the well-deserved retirement of lab-manager Anne Pharo, who has been instrumental in establishing all current methods in the group and especially those related to experimental animal models. Although Anne will be greatly missed by all group-members, she leaves a strong and solid foundation for smooth running of the lab that we will build on in the years to come. We wish her a very happy retirement.

In June the INFLAMMABILE grant was funded by the Research Council of Norway grant with 12 mill NOK. In this project we will examine bile duct inflammation in PSC patients and mouse models at different time points using spatial sequencing and 3D immunohistochemistry. The grant was a collaboration with Brian Chung in the genomics group at NoPSC and the grant now funds a senior scientist position in the experimental group that Brian started in December. Markus Jördens joined the team working on sequencing based techniques in September as a PhD student funded by the German Krebshilfe foundation and his project will also encompass examination of the spatial transcriptome of cholangiocarcinoma.

Haemostasis, Thrombosis, and Vascular Biology Research

From left: Adelheid Holm, Nina Haagenrud Schultz, Pål André Holme, Ragnhild J. Måseide, Christian Qvigstad and Ruth Elise Dybvik Matlary.



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Research profile Sandset/Stavik:

"Coagulation Factors: Role in the Development of Thrombosis, Inflammation and Cancer"

The main goal of this research group is to identify how and why coagulation proteins contribute to or prevent disease, and to utilize this knowledge to improve patient care.

Blood coagulation is important for maintaining a healthy blood flow and can contribute to disease in several ways: 1) Anomalies in coagulation proteins cause pathological bleeding or thrombosis. 2) Common diseases such as infarctions, sepsis (a systemic inflammatory reaction), and cancer are manifested by thrombotic complications. 3) Coagulation proteins facilitate progression of inflammation and cancer independent of blood coagulation.

Deeper knowledge about the biology of coagulation proteins is therefore important not only in the care for haemostatic disorders, but also in preventing the morbidity and mortality of other common diseases.

We therefore conduct basic, translational, and clinical research with focus on gene mutations, molecular and biological activities and haemostatic function in in vitro and in vivo systems and in ex vivo samples.

Activity in 2021:

Coagulation factor deficiency and liver cell models
Inherited deficiency in coagulation factor (F) VII can cause mild and severe bleeding in affected individuals. The deficiency is caused by mutations in the corresponding *F7* gene that results in reduced or diminished activity if the factor or inhibitor in plasma. FVII is produced in the liver and secreted to plasma and we have therefore utilized stem cell differentiation techniques to generate stem cell derived livers cells and organoids in the lab to model production and secretion. In one project we have been investigating the possibility to correct the *F7* gene mutation with CRISPR-CAS9 gene editing, using patient-derived stem cells and in 2021 we got additional funding for moving this project into the pre-clinical stage. In another project, we are using the same liver cell models to investigate the molecular cause of antithrombin (AT) deficiency, a deficiency in the coagulation inhibitor AT due to a mutation in the corresponding gene that cause thrombotic events.

Drug repurposing
Drug repurposing has become a valuable tool to find new treatments to various diseases with low cost and little time. Previous findings in our lab indicated that an approved drug was able to increase the activity of mutated FVII. We therefore performed a larger screen using >1000 FDA approved drugs to identify potential compounds. The screen identified two hits, and we are now in the process of confirming these in *in vitro* and *ex vivo* studies.

Coagulation proteins in atherosclerotic disease
Atherosclerosis is an inflammatory disease that culminates in thrombotic complications. Using a biobank of human carotid plaques, we are looking into the presence of coagulation factors inside the plaque and investigate their potential role in regulating inflammation and plaque development. The aim is to identify regulatory targets that can reduce the inflammatory burden and, potentially, be beneficial in attenuating atherothrombosis.

Haematological malignancies The coagulation factor inhibitor Tissue Factor Pathway Inhibitor (TFPI) has been shown to play a role in cell migration, at least partly by regulating CXCLR4 receptor levels. Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the western world and CXCLR4 is considered a major regulator of trafficking and homing of CLL cells. However, in this project we discovered that TFPI induced expression of another mitotic receptor, CXCLR7, which in turn increased the CXCL12 induced migration of the patient leukemia cells. Consistent with this we found increased TFPI levels in plasma of according to the severity of the illness. This work was published last year in Scientific Reports. In another project, that was started up in 2021, we are using single cell sequencing to map coagulation protein expression in the bone marrow of patients with different stages of multiple myeloma (MM). These patients are prone to cancer-related thrombosis and we are looking for possible explanations in the tumour microenvironment. Preliminary data are showing promising results.

Coagulation factors and breast cancer
We have in previous settings shown that oestrogens regulate the expression of several coagulation proteins and in oestrogen responsive breast tumours, oestrogen signalling plays an important role in the development of the disease. We know that breast cancer patients have increased risk of developing thrombosis and that pro-thrombotic proteins are elevated in some breast tumours. In one project, we have been investigating whether oestrogen can affect the expression of coagulation factor V (FV) in an oestrogen responsive breast cancer cell line. We found that oestrogen bind to specific sites in the promotor sequence of the *F5* gene and regulate its expression. Also, through mining public databases online we found that patients with oestrogen responsive breast cancers that have high levels of FV in the tumour, are associated with prolongs survival. These findings were published last year in Thrombosis and Haemostasis.

Characterization of coagulation markers in clinical samples
The group is involved in a number of clinical studies in collaboration with local and national/international clinicians and researchers and is responsible for the analysis of coagulation related biochemical markers in these studies. In 2021 we participated in a large, national study investigating haematological parameters in health care workers following COVID-19 vaccination.

Research profile Holme:

"Haemostasis and Bleeding Disorders"
Our scientific interests are focused on clinical and basic aspects of normal and disturbed haemostasis in particular bleeding disorders like hereditary and acquired coagulation disorders.
Oslo University hospital, Rikshospitalet is the only Haemophilia Comprehensive Care Centre in Norway and is one of the biggest haemophilia centres in the Nordic region taking care of more than 1200 persons with bleeding disorders. Several research projects are ongoing besides clinical activity.

Activity in 2021:

Moderate haemophilia
Current treatment of haemophilia is predominantly guided by the severity classification. While patients with severe haemophilia are closely monitored and receive early prophylaxis, moderate and mild patients are monitored less frequently and mostly receive treatment on-demand. The group of moderate haemophilia, however, is heterogeneous with a wide variation in clinical phenotype, with some of the patients having a considerable need for factor substitution. Bleeding phenotype is not strictly correlated to the coagulation factor level, but also influenced by physical activity, presence of target joints and synovial hypertrophy, degree of arthropathy and adherence to a prophylactic regime. According to more recent thinking, haemophilia care and treatment therefore should be tailored individually. PhD student Ragnhild J Måseide has studied and evaluated the treatment and joint health in Nordic moderate haemophilia patients (haemophilia A and B) (factor level 1-<5 IU/dL) in the Nordic region to explore if they receive optimal care. The study has enrolled 145 pts. She has submitted her thesis entitled: Moderate haemophilia A and B in the Nordic countries – The MoHem study for public defence that will take part in Feb 2022. Three papers have been published from the study

Age related comobidities in haemophilia
Rates of hypertension and renal disease, as with other cardiovascular risk factors and comorbidities, are known to rise with age. In haemophilia, it appears from some reports that there is an even stronger association with hematuria and hypertension. Our group is the coordinating centre for an epidemiologic European multicentre study on behalf of the ADVANCE (Agerelated-DeVelopments-ANd-Comorbidities-in-hemophilia Working Group)
The group is interested in determining, among consecutively screened people with haemophilia (800 pts.), aged ≥40 years with a follow up period of 10 years, whether rates of hypertension and renal disease vary according to a previous history of hematuria and whether rates of hypertension/renal disease/ and other cardiovascular and malignant comorbidities vary with specific influencing factors in haemophilia. Four papers from the cross-sectional study have already been published and now further followed up in the longitudinal prospective study.

Optimizing bypassing agents.
During the last years we have studied and published papers on how to optimize and tailor treatment in persons with haemophilia with or without inhibitors to FVIII and in persons with FVII deficiency.
One of main objectives has been tailoring of treatment with bypassing agents (BPA) for haemophilia patients with inhibitors. Development of inhibitors is the most serious complications of haemophilia treatment today, High titre inhibitors to factor VIII and less often to factor FIX, represent a major challenge in the treatment of haemophilia A and B. The treatment of bleeds in haemophilia patients with inhibitors relies on the use of the bypassing agents, factor eight bypassing activity (FEIBA) or recombinant factor VIIa. While both therapies are effective in the majority of bleeding episodes and postoperative prophylaxis, there is a significant amount of inter individual variability when it comes to the response to therapy. During the last year emicizumab have been introduced to many of our haemophilia patients with inhibitors as prophylactic treatment. When these persons need to undergo major surgery etc monitoring of the haemostatic effect is essential since we need to use concomitant treatment with BPA.
In haemophilia patients without inhibitors, there is a close relationship between the level of FVIII or FIX measured ex vivo and the haemostatic outcome of the patients.
However, in inhibitor patients there is no such relationship using bypassing treatment as there is no established laboratory assay to monitor efficacy and optimal dosing.
We are studying the effect of bypassing agents with or without concomitant treatment of emicizumab using thromboelastography (TEG/ ROTEM) and thrombin generation test (TGA) to individualize coagulation factor concentrate usage and dosing in the home treatment program, individualize coagulation factor concentrate usage and dosing prior to and in the postoperative period, address the issue of minimum effective dose during surgery and apply these assays in the evaluation of the critically ill patient with concomitant haemostatic insufficiency. In addition, we have published that adjunct use of tranexamic acid (TXA) to BPA significantly increased the clot stability without increasing the thrombin generation and may be superior to standard treatment with BPA alone.

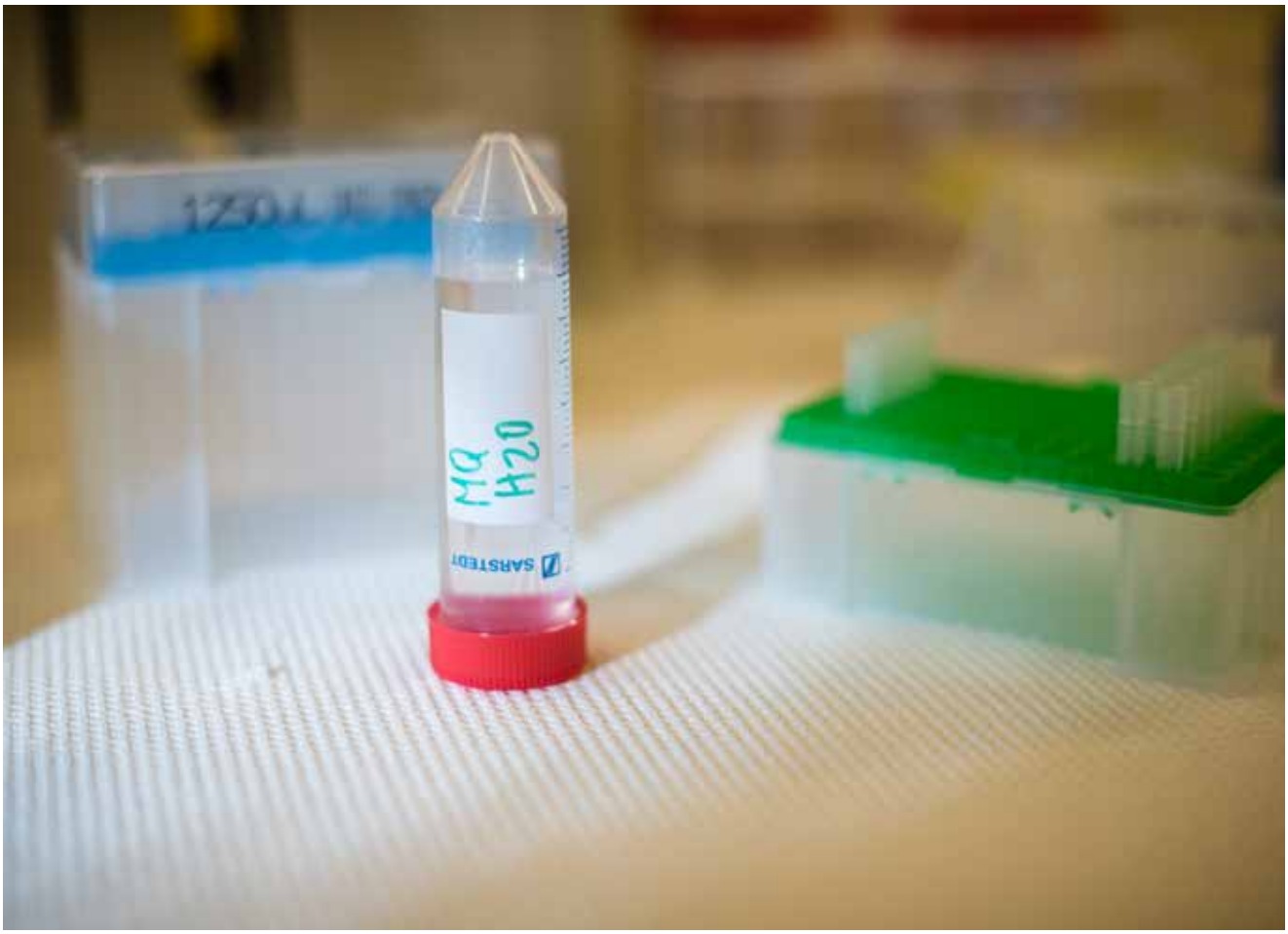
Reversal of factor Xa inhibitors
Today there are no available, evaluated effective treatments to reverse the effect of FXa-inhibitors (direct oral anticoagulants (DOAC)). We have performed studies where the objectives were to detect the most effective haemostatic agent (activated prothrombin complex concentrate (aPCC), prothrombin complex concentrate (PCC) and rFVIIa and appropriate dose for reversal of bleeds caused by FXa inhibitors extensively used in the clinic for atrial fibrillation and treatment of venous thromboembolism. The effect was assessed mainly by the two global coagulation methods thromboelastography (TEG) and thrombin generation assay (TGA). Five papers on this subject have been

published and Nina Haagenrud Schultz defended her thesis entiteled: "Oral factor Xa inhibitors: Studies on reversal of their anticoagulant effect and on their influence on primary hemostasis endothelial function and fibrinolysis." November 2019 and further studying new aspects as a post doc.

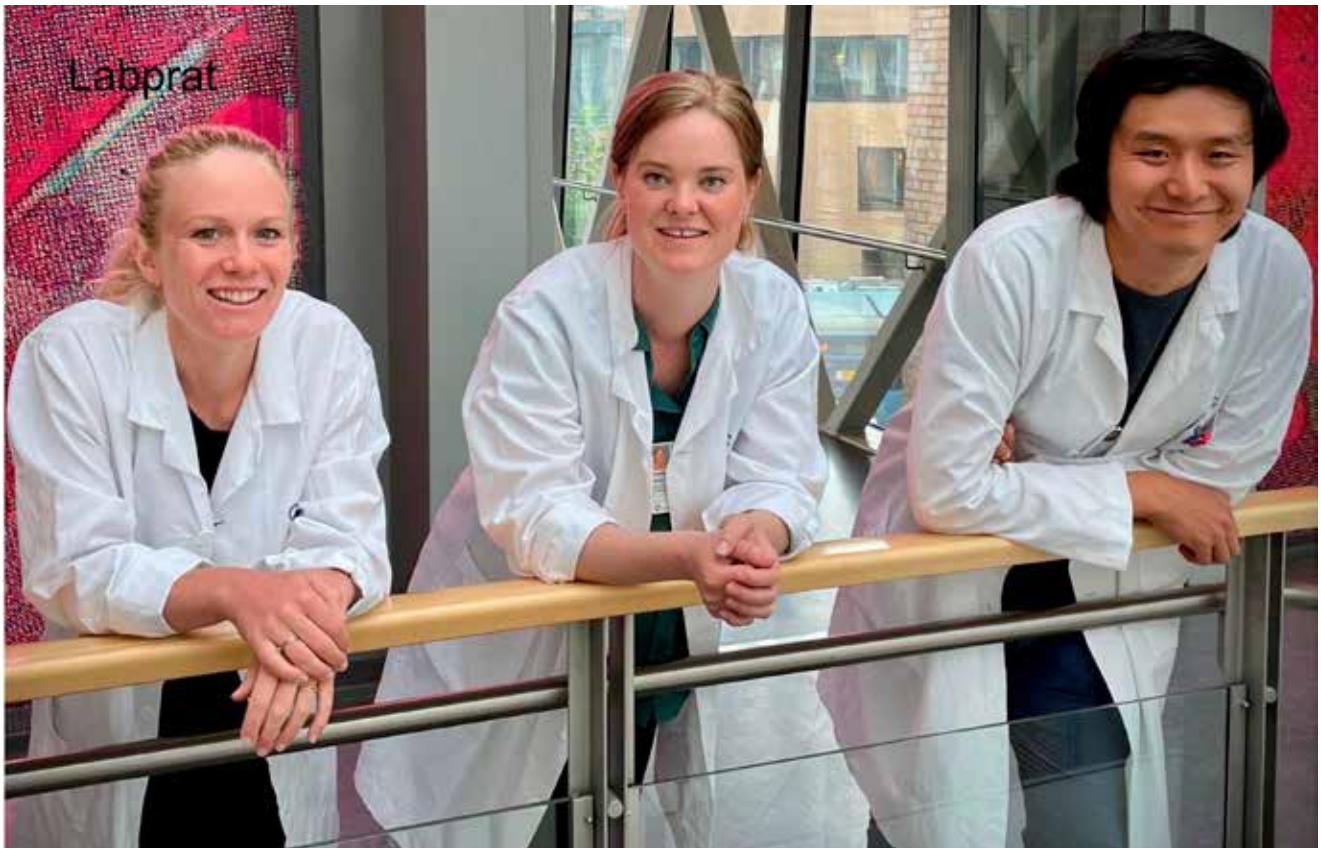
HemFitBit study- Defining Normal Activity in Hemophilia
There is a lack of knowledge regarding how physically active people with the bleeding disorder haemophilia A are compared to controls without haemophilia. This project has collected information on physical activity levels in 40 patients with haemophilia A aged 12-30 years over a 3-month period using the wearable technology 'Fitbit'. A subgroup of participants has also wear the accelerometer 'ActiGraph' in order to validate the two devices against each other.
The study data are being compared with pre-existing age-, region- and season-matched controls. This information is now being analysed to see if there are any relationships between these factors and level and intensity of physical activity. One hypothesis is that the registered physical activity level can be used as a surrogate outcome measure to the number of bleeds per year (annual bleeding rate) which is currently the most utilised outcome measure, although considered an uncertain subjective endpoint. Ruth Elise Dybvik Matlary, MSc is working as a PhD student on this project.

VITT- Vaccine-induced immune thrombotic thrombocytopenia
From March 2021 the group has worked extensively on the SARS-CoV-2 vaccination-related thrombotic complications and thrombocytopenia giving devastating adverse events. This has been done in close collaboration with other groups here at RIIM and Department of immunology, OUS and the Norwegian National Unit for Platelet Immunology, Division of Diagnostics, University Hospital of North Norway. This work lead to the first main publications:
Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384: 2124-30
Immune Complexes, Innate immunity, and NETosis in ChadOx1 vaccine-induced thrombocytopenia. Eur Heart J. 2021; 42:4064-72.

Immune thrombocytopenia
Parts of the group is also involved in studies on immune thrombocytopenia ITP and in the RITP trail we aimed to assess the efficacy of rituximab as compared with placebo as a splenectomy-sparing treatment in patients who were previously treated with corticosteroids. (Lancet 2015; 385: 1653–61). The follow up study PROLONG has now been ongoing for 6 years where we want to evaluate the long-term effect of rituximab and immunological changes also including a PhD project on the immunological. The group also participates in several other international and Nordic investigator-initiated research projects on bleeding disorders.



PUBLIC OUTREACH



Labprat

During 2021, three of our colleagues, Ida Gregersen, Maria Belland Olsen and Xiang Yi Kong established the podcast “Labprat”. The podcast was started with a desire to reach out with research and knowledge dissemination to the general public, and that it can be used as an advertising or recruitment method for scientific and medical studies. At the same time, parts of research life and research in general that do not always appear in public is presented. It’s rarely just scandals or just magical discoveries, but also a lot of trial and errors and hidden bureaucracy. The podcast is available for download from most platforms, and is already established among the most popular in its field here in Norway.

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Aftenposten
Onsdag 5. mai 2021

Replikk

Næringsutvikling og statens rolle

I Aftenposten 3. mai skriver Trygve Tamburstuen i et svar til meg at «all erfaring nasjonalt og internasjonalt viser at utvikling av nye næringer krever selektive og målrettede virkemidler, noe blant annet den ulyre vellykkede utviklingen av den norske petroleumsnæringen viser».

Jeg vet ikke hva Tamburstuen mener med «selektive og målrettede virkemidler», men det kunne vært veldig interessant å høre om den omfattende erfaringen Tamburstuen sikter til. La meg i den forbindelse minne om at det vi diskuterer, er selektive subsidietiltak og etablering av statseierskap innenfor umodne næringer med svært usikker lønnsomhet.

At petroleumsnæringen fremstår som et godt eksempel på en slik politikk, er vanskelig å forstå. Det var utenlandske selskaper som først fant olje i Nordsjøen. Statoil ble etablert lenge etter at det var klart at olje var en svært ettertraktet ressurs. Det var ikke unikt for Norge å ha et statsoljeselskap, og næringen ble ikke subsidiert frem.

At oljeeventyret også kom Norge og befolkningen til gode, skyldes at politikerne sikret et godt regulerings- og skatteregime, konkurranse på sokkelen og en fornuftig forvaltning av rikdommen. Om vi kunne fått enda mer ut av eventyret dersom Statoil hadde vært privat eller delprivatisert for, er det ingen som i dag kan vite.

Kristin Clemet,
leder i Civita

Tør vi å snakke om covid-19 og genetikk?

Debatt

Sheraz Yaqub, førsteamanuensis, Universitetet i Oslo og overlege, Oslo universitetssykehus

Mohammad Usman Rana, lege, Oslo universitetssykehus

Tom Hemming Karlsen, professor, Universitetet i Oslo og overlege, Oslo universitetssykehus

Det er mye bekymring og frykt i nyhetsbildet omkring covid-19, enten det gjelder de siste smittetallene, virusmutanter eller samlinger av ungdom som vil nyte våren ute i Oslos parker. Det finnes også emner vi har vært redde for å ta opp, av frykt for å stigmatisere enkeltgrupper.

Folkehelseinstituttet (FHI) ga tidligere i april ut en rapport om covid-19 blant personer født i utlandet. Tallene var justert for yrke, trangboddhet, medisinsk risikogruppe og inntekt.

Bakgrunnen er at utenlandsfødte er sterkt overrepresentert når det gjelder smitte og sykehusinnleggelser. FHIs rapport konkluderer med at overrepresentasjonen i liten grad forklares av deres utvalg av sosioøkonomiske faktorer og medisinske risikogrupper.

Basert på de nyeste dataene fra England er vi nok noe skeptiske til robustheten i denne konklusjonen. Men forutsatt at FHIs analyser er korrekte, må det letes etter andre forhold som kan forklare overrepresentasjonen.

Adferd og genetikk

To nøkkelord er adferd og genetikk. Når det gjelder det siste, mener vi FHIs rapport ikke følger dette sporet i nevneverdig grad. De baserer seg langt ifra på den nyeste forskningen på feltet.

Faktisk nevner ikke FHIs rapport med ett ord den norskledede studien som for første gang i verden påviste genetisk risiko for covid-19, publisert i *New England Journal of Medicine* allerede i juni i fjor.

Kanskje har man gått glipp av denne på grunn av oppmerksomheten i mediene? Der ble det begeistret lagt all vekt på en «fun fact» som tyder på at folk med blodtype O har mindre risiko for å bli smittet av koronavirus. Mens aviser og sosiale medier var opptatt med denne biologiske kuriositeten, lusket hovedfunnet i studien rundt i skyggene. Et mer anonymt genområde på kromosom 3 drev med sine ting: å gi alvorlig sykdom og død hos personer som ble infisert med koronaviruset.

Bekreftet av andre studier

Begge disse funnene er nå solid bekreftet av tallrike andre studier. For «hovedgenet» på kromosom 3 er effekten i genetisk forstand formidabel: Mens man i europeiske befolkningsgrupper normalt finner denne risikovarianten hos 14 prosent, finner man den hos 32 prosent av unge europeere (under 60 år) som får alvorlig covid-19 med sykehusinnleggelse og død.

Poenget er at allerede i studien fra juni i fjor pekte forskerne på at genfunnet kunne føre til forskjeller i hvor alvorlig ulike folkegrupper blir rammet av covid-19.

Om vi for eksempel ser på sørasiatiske befolkninger, som omfatter blant andre India og Pakistan, er denne genvarianten normalt til stede hos omtrent halvparten av friske individer, mot altså normalt ca. 14 prosent hos europeere. Interessant nok finnes genvarianten praktisk talt ikke hos kinesere og lenger øst i Asia.

> **Vi synes det er noe overraskende at FHI ser på genetikk som en lite sannsynlig årsak til å forklare overrepresentasjon for sykehusinnleggelser**

Vi synes derfor det er noe overraskende at FHI ser på genetikk som en lite sannsynlig årsak til å forklare overrepresentasjon for sykehusinnleggelser.

Vaksinestrategi

Vi må ikke glemme at det norske utvalget er lite og uegnet til å trekke bastante konklusjoner. Dersom man ser til Storbritannia, et land med store minoriteter med opprinnelse fra India, Pakistan og Bangladesh, ser man at det er små forskjeller mellom personer med indisk eller pakistansk opphav. Begge grupper er ettertrykkelig overrepresentert på dystre covid-19-statistikker. Og hvordan covid-19 oppfører seg i India, får vi nå dessverre daglige påminnelser om.

Vi mener at genetisk sårbarhet er en plausibel forklaring på hvorfor nordmenn med opphav fra Sør-Asia er ekstra hardt rammet og ofiere blir innlagt på sykehus med covid-19. Helsemyndighetene bør ta disse funnene i betraktning når de skal vurdere risikogrupper i vaksinestrategien, både for å få ned smitten og også i andre tiltak for å få ned antall sykehusinnleggelser.

Ellers har vi understreket, deriblant i en kronikk i Aftenposten i påsken, at sårbare minoriteter må være ekstra påpasselige med sin adferd for å unngå smitte. Og de bør absolutt følge vaksinasjonsrådene.

En indisk mann blir testet for koronaviruset. India er hardt rammet av en ny smittebølge. Gener kan være en del av forklaringen, skriver artikkelforfatterne.
Foto: Anupam Nath, AP/NTB

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